IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Robert M. Townsend et al.	Examiner:	Phillip Gambel, Ph.D.
Serial No.:	09/877,987	Group Art Unit:	1645
Filed:	June 8, 2001	Docket:	D0009NP; 30436.53USU1
Title:	METHODS FOR REGULATING A CELL-MEDIATED IMMUNE RESPONSE BY BLOCKING LYMPHOCYTIC SIGNALS AND BY BLOCKING LFA-1-MEDIATED ADHESION		

CERTIFICATE UNDER 37 CFR 1.8
I hereby certify that this paper or fee is being deposited with the United States Postal as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on January 14, 2003.

By: _____
Name: Tracy Truick

55 South Lake Avenue, Suite 710
Pasadena, California 91101
January 14, 2003

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

- ☒ Transmittal Sheet in duplicate containing Certificate under 37 C.F.R. 1.8
- ☒ Supplemental Information Disclosure Statement (37 C.F.R. §1.97(b))
- ☒ Form 1449 (Information Disclosure Statement)
- ☒ Exhibits 88-189
- ☒ Return postcard

Please charge any and/or additional fees or credit overpayment to Deposit Account No. 50-0306. A duplicate of this sheet is enclosed.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Robert M. Townsend, et al.	**Examiner:**	Phillip Gambel, Ph.D.
Serial No.:	09/877,987	**Group Art Unit:**	1644
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By: Tracy Truick

55 South Lake Avenue
Suite 710
Pasadena, California 91101
January 14, 2003

SUPPLEMENTAL INFORMATION
DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b) 3))

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

This Information Disclosure Statement is being filed herewith as a supplement to Applicant's October 26, 2001, Information Disclosure Statement which was submitted under 37 C.F.R.§1.97 (b) before the mailing date of the first Office Action on the merits. In accordance with 37 C.F.R. §1.98(d), copies of Exhibits 88-189 as set forth in the Form 1449 are included herewith.

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- Linsley, et al., 1991, *J.Exp.Med.*"CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" 174:561-569. **(Exhibit 88)**

- Gimmi, et al., 1993, *Proc.Natl.Acad.Sci. USA* "Human T-Cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" 90:6586-6590. **(Exhibit 89)**
- Azuma et al., 1993 *Nature* "B70 antigen is a second ligand for CTLA-4 and CD28" 366:76-79. **(Exhibit 90)**
- Ronchese et al., 1994 *J.Exp.Med* "Mice Transgenic for a Soluble Form of Murine CTLA-4Show Enhanced Expansion of Antigen-specific CD4 T Cells and Defective Antibody production In Vivo" 179:809-817. **(Exhibit 91)**
- Griggs et al., 1996 *J.Exp.Med* "The Relative Contribution of the CD28 and gp39 Costimulatory pathways in the Clonal Expansion and Pathgenic Acquistion of Self-reactive T Cells" 183:801-810. **(Exhibit 92)**
- Verwilghen et al., 1994 *J-Immunol.* Expressionof Functional B& and CTLA4 on Rheumatoid Synovial T Cells" 153:1378-1385. **(Exhibit 93)**
- Blazar et al., 1994 *Blood* "In Vivo Blockade of CD28/CTLA4: Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatiblity Complex Barrier in Mice" 83:3815-3825. **(Exhibit 94)**
- Finck et al., *Science* "Treatment of Murine lupus with CTLA4Ig" 265:1225-1227. **(Exhibit 95)**
- Perrin et al., 1995 *J-Immunol* "Role of B7:CD28/CTLA4 in the Induction of Chronic Relapsing Experimental Allergic Encephalomyelitis" 154:1481-1490. **(Exhibit 96)**
- Pearson et al., 1994 *Transplantation* "Transplantation Tolerance Induced By CTLA4-Ig" 57:1701-1706. **(Exhibit 97)**
- Baliga et al., 1994 *Transplantation* "CTLA4Ig PROLONGS ALLOGRAFT SURVIVAL WHILE SUPPRESSING CELL-MEDIATED IMMUNITY" 58:1082-1090. **(Exhibit 98)**
- Tepper et al., 1994 *Transplantation Proceedings* "Tolerance Induction by soluble CTLA4 in a Mouse Skin Transplant Model" 26:3151-3154. **(Exhibit 99)**

- Perico et al., 1995 *Kidney International* "Toward novel antirejection strategies: In *vivo* immunosuppressive properties of CTLA4Ig" 47:241-246. **(Exhibit 100)**
- Finck et al., 1994 *Arthritis and Rheumatism* "Effects of CTLA4Ig in murine lupus" 37:S222. **(Exhibit 101)**
- Nishikawa et al., 1994 *Eur J. Immunol.* "Effect of CTLA-4 chimeric protein on rat autoimmune anti-glomerular basement membrane glomerulonephritis" 24:1249-1254. **(Exhibit 102)**
- Wallace et al., 1994 *Transplantation* "CTLA4ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers" 58:602-610. **(Exhibit 103)**
- Damle et al., *J. Immunol.* "Costimulation of T Lymphocytes with integrin Ligands intercellular Adhesion Molecule-1 or Vascular Cell Adhesion Molecule-1 Induces Functional Expression of CTLA-4, a Second Receptor for B7" 152:2686-2697. **(Exhibit 104)**
- Milich, et al., 1994 *J. Immunol* "Soluble CTLA-4 can suppress autoantibody production and elicit long term unresponsiveness in a novel transgenic model," 153:429-435. **(Exhibit 105)**
- Webb, et al., 1996 *Eur J. Immunol* "Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2," 26:2320-2328. **(Exhibit 106)**
- Van Oosterhout, et al., 1997 *Am.J.Respir.Cell Mol.Biol* ."Murine CTLA4-IgG Treatment Inhibits Airway Eosinophilia and Hyperresponsiveness and Attenuates IgE Upregulation in a Murine Model of allergic Asthma," 17:386-392. **(Exhibit 107)**
- Abrams et al., 1999 *J-Clin-Invest* "CTLA4Ig-mediated blockade of T-cell costimuation in patients with psoriasis vulgaris. 103:1243-1252. **(Exhibit 108)**
- Ibrahim, et al., 1996 *Blood* "CTLAIG Inhibits Alloantibody Responses to Repeated Blood Transfusions," 88:4594-4600. **(Exhibit 109)**

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- Hochberg, et al., 1990 *Epidemiologic Reviews* "Epidemiology of Rheumatoid Arthritis: Update," 12:247-252. **(Exhibit 114)**
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- Pearson TC, Alexander DZ, Winn KJ, Linsley PS, Lowry RP, Larsen CP, 1994. "Transplantation tolerance induced by CTLA4-Ig. *Transplantation*, 57:1701-1706. **(Exhibit 122)**
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- Aruffo, S., March 27, 2000, Presentation of "Approaches to Immune Regulation" at BIO 2000 in Boston, Mass. **(Exhibit 132)**
- Abrams, et al., September 4, 2000, *J.Exp.Med.* "Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte- associated Antigen 4-Immunogloblin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells, " 192:681-693. **(Exhibit 133)**
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- Flesher, A.R., April 15, 1999, *Biological Process Sciences* Presentation of 'Transgenic Production, A Comparative Study" at Bio 99 in Seattle, Washington. **(Exhibit 136)**
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- Weiner, R.S., November 1995 Abstract and Presentation of "Validation of an Enzyme Immunoassay For The Quantition of Human CTLAIg Fusion Protein In Human Serum," in Miami, Florida. **(Exhibit 143)**
- Weiner, R.S., November 1995 Abstract and Presentation of "Automation and Validation of An EIA For Quantition of Human CTLAIg In Monkey Serum," in Miami, Florida. **(Exhibit 144)**
- Webb, L.M.C. et al., July 23, 1996 *Eur J Immunol* "Prevention and amelioration of collagen-induced arthritis by blocade of the CE28 co-stimulatory pathway: requirement for both B7-1 and B7-2" 26:2320-2328. **(Exhibit 145)**
- Knoerzer, et al., May 5, 1995, *J Clin. Invest* "Collagen-induced Arthritis in the BB Rat Prevention of Disease by Treatment with CTLA4Ig" 96:987-993. **(Exhibit 146)**

- Larsen, et al., April 27, 2000, Abstract of "Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-IG Fusion Protein In Non-Human Primates," in *Transplantation,* 69(8): #44, p. S123, Chicago, Il. **(Exhibit 147)**
- Larsen, et al., May 13-17, 2000, A Presentation of "Prolongation of Renal Allograft Survival With Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-Ig Protein In Nonhuman Primates" at the American Society of Transplantation Meeting in Chicago, Il. **(Exhibit 148)**
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- Larsen, March 3-4, 2000, A Presentation of "Costimulation blockade: progress toward clinical application" at Canadian Society of Transplantation Annual Scientific meeting in Mont Tremblant, Quebec, Canada. **(Exhibit 150)**
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- Hathcock, et al., August 30, 1993 *Science* "Identification of an Alternative CTLA-4 Ligand Costimulatory for t Cell Activation," 262:905-911. **(Exhibit 152)**
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- U.S. Patent No. 5,434,131, July 18, 1995. **(Exhibit 154)**
- PCT No. WO 02/02638 A2, January 10, 2002. **(Exhibit 155)**
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- Alexander, Diane Z., "ANALYSIS OF A FUNCTIONAL ROLE FOR CHIMERISM IN CTLA4-Ig PLUS BONE MARROW-TREATED CARDIAC ALLOGRAFT RECIPIENTS," *Transplantation,* 1994, 91:416-418. **(Exhibit 159)**
- Larsen, Christian P., et al., "CD40-gp39 INTERACTIONS PLAY A CRITICAL ROLE DURING ALLOFRAFT REJECTION" *Transplantation,* 1996, 61:4-9. **(Exhibit 160)**
- Pearson, Thomas C., et al., "CTLA4-Ig PLUS BONE MARROW INDUCES LONG-TERM ALLOGRAFT SURVIVAL AND DONOR-SPECIFIC UNRESONSIVENESS IN THE MURINE MODEL", *Transplantation,* 1996, 61:997-1004. **(Exhibit 161)**
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- Larsen, Christian P., and Thomas C. Pearson., "The CD40 pathway in allograft rejection, acceptance, and tolerance," *Transplantation,* 1997, 9:641-647. **(Exhibit 166)**
- Konieczny, Bogumila T.., et al., "IFN-γ Critical for Long-Term Allograft Survival Induced by Blocking the CD28 and CD40 Ligand T Cell Constimulation Pathways[1]," *The Journal of Immunology,* 1998, 160:2059-2064. **(Exhibit 167)**

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- Niimi, Masanori, et al., "The Role of the CD40 Pathway in Alloantigen-Induced Hyporesonsiveness in Vivo1," The Journal of Immunology, 1998,161:5331-5337. **(Exhibit 169)**
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- Bingaman, Adam W., et al., "Vigorous Allograft Rejection in the Absence of Danger1," Journal of Immunology, 2000,164:3065-3071. **(Exhibit 171)**
- Bingaman, Adam W., et al., "TRANSPLANTATION OF THE BONE MARROW MICROENVIROMENT LEADS TO HEMATOPPIETIC CHIMERISM WITHOUT CYTOREDUCTIVE CONDITIONING," Transplantation, 2000, 69:2491-2496. **(Exhibit 172)**
- Durham, Megan M., et al., "Cutting Edge: Administration of Anti-CD40 Ligand and Donor Bone Marrow Leads to Hemapoietic Chimerism and Donor-Specific Tolerance Without Cytoreductive Conditioning[1]," *Cutting Edge,* 2000, 165:1-4. **(Exhibit 173)**
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- Bingaman, Adam W., et al., "The role of CD40L in T cell-dependent nitric oxide production by murine macrophages," *Transplant Immunology,* 2000, 8:195-202. **(Exhibit 175)**
- Adams, Andrew B., et al., "Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct

Genetic Hemoglobinopathies with Minimal Myelosuppression[1]," *The Journal of Immunology,* 2001, 167:1103-1111. **(Exhibit 176)**

- Meng, L., "Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection," *Transplantation Proceedings,* 2001, 33:418-420. **(Exhibit 177)**
- Guo, Zhong., et al., "CD8 T CELL-MEDIATED REJECTION OF INTESTINAL ALLOGRAFTS IS RESISTANT TO INHIBITION OF THE CD40/CD154 COSTIMULATORY PATHWAY," *Transplantation,* 2001, 71:1351-1354. **(Exhibit 178)**
- Ha, Jongwon., et al., "Aggressive skin allograft rejection in $CD28^{-/-}$ mice independent of the CD40/CD40L costimulatory pathway," *Transplant Immunology,*2001, 9:13-17. **(Exhibit 179)**
- Bingaman, Adam W., et al., "ANALYSIS OF THE CD40 AND CD28 PATHWAYS ON ALLOIMMUNE RESPONSES BY $CD4^+$ T CELLS IN VIVO[1]," *Transplantation,* 2001, 72:1286-1292. **(Exhibit 180)**
- Adams, Andrew B., et al., "Calcineurin Inhibitor- Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates," *Diabetes,* 2002, 51:265-270. **(Exhibit 181)**
- Whelchel, JD., et al. "Evolving Strategies in immunosuppressive Therapy: The Emory Experience," *Clinical Transplants*, 1996, 20:249-255 **(Exhibit 182)**
- Ritichie, SC., et al., "Regulation of Immunostimulatory function and B7 molecule expression on murine dendritic cells," *Journal of Cellular Biochemistry,*1995,21A:C1-215**(Exhibit 183)**
- Alexander, DZ., et al., "Analysis of the mechanisms of CTLA4-Ig plus bone marrow induced transplantation tolerance," *Journal of Cellular Biochemistry*, 1995, 21A:C1-301 **(Exhibit 184)**

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- Pearson, TC., et al., "CTLA4-Ig plus bone marrow induces transplantation tolerance in the murine model," Journal of Cellular Biochemistry, 1995, 21A:C1-327 **(Exhibit 186)**
- Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," Journal of the American Society of Nephrology, 1996, 7:A3204 **(Exhibit 187)**

- L104EA29Y (Figure 6, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
- L104EA29Y (Figure 6 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.
  - L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
  - L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
- A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 188**.
  - The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R.§20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation

and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.

- The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
- The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 188), which differs from CTLA4Ig at two amino acid residues, Leu_{104}-Glu and Ala_{29}-Tyr (Exhibit 188 at page 2).

- An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 189**.
  - The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
  - The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
  - The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 189), but not the sequence of L104EA29Y (Figure 6, of the subject application).

No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the references are not "prior art." Applicants wish to reiterate that the documents and information above were not at the time of filing publicly available since they were provided under confidentiality agreements.

Consideration of the items listed is respectfully requested. Applicants invite the Patent Office to request additional information if necessary. Pursuant to the provisions of M.P.E.P. 609, it is

Consideration of the items listed is respectfully requested. Applicants invite the Patent Office to request additional information if necessary. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,

Sarah B. Adriano
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FORM 1449*	Docket Number	Application Number
INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION	D0009NP;30436.53USU1	09/877,987
	Applicant	
	Robert M. Townsend et al.	
(Use several sheets if necessary)	Filing Date	Group Art Unit
	June 8, 2001	1645

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE
	5,434,131 **(Exhibit 154)**	7/18/95	Linsley et al.			5/26/93

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
	WO 95/33770 **(Exhibit 124)**	12/14/95	PCT				X
	WO 02/02638 A2 **(Exhibit 155)**	1/10/02	PCT				X

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

		Linsley, et al., 1991, *J.Exp.Med.*"CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" 174:561-569. **(Exhibit 88)**
		Gimmi, et al., 1993, *Proc.Natl.Acad.Sci. USA* "Human T-Cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" 90:6586-6590. **(Exhibit 89)**
		Azuma et al., 1993 *Nature* "B70 antigen is a second ligand for CTLA-4 and CD28" 366:76-79. **(Exhibit 90)**
		Ronchese et al., 1994 *J.Exp.Med* "Mice Transgenic for a Soluble Form of Murine CTLA-4Show Enhanced Expansion of Antigen-specific CD4 T Cells and Defective Antibody production In Vivo" 179:809-817. **(Exhibit 91)**
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		Larsen, Aug. 27-Sept.1, 2000, A Presentation of "Manipulation of Costimulatory Pathways: Targeting CD80 and CD86" at the XVII congress of the Transplantation Society in Rome, Italy. **(Exhibit 149)**
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		Adams, Andrew B., et al., "Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct Genetic Hemoglobinopathies with Minimal Myelosuppression[1]," *The Journal of Immunology,* 2001, 167:1103-1111. **(Exhibit 176)**
		Meng, L., "Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection," *Transplantation Proceedings,* 2001, 33:418-420. **(Exhibit 177)**
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		Whelchel, JD., et al. "Evolving Strategies in immunosuppressive Therapy: The Emory Experience," *Clinical Transplants,* 1996, 20:249-255 **(Exhibit 182)**
		Ritichie, SC., et al., "Regulation of Immunostimulatory function and B7 molecule expression on murine dendritic cells," *Journal of Cellular Biochemistry,*1995,21A:C1-215**(Exhibit 183)**
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		Pearson, TC., et al., "CTLA4-Ig plus bone marrow induces transplantation tolerance in the murine model," Journal of Cellular Biochemistry, 1995, 21A:C1-327 **(Exhibit 186)**
		Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," Journal of the American Society of Nephrology, 1996, 7:A3204 **(Exhibit 187)**
		L104EA29Y (Figure 6, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
		L104EA29Y (Figure 6 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.

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		L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
		L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
		A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 188.**
		The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R.§20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
		The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
		The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 171), which differs from CTLA4Ig at two amino acid residues, Leu104-Glu and Ala29-Tyr (Exhibit 171 at page 2).
		An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 189**.
		The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
		The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
		The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 172), but not the sequence of L104EA29Y (Figure 6, of the subject application).

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